Klaylan MacChase
384 Chapin Ct.
Cradell, New Jersey 07649
August 14, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn St. Rm. 1-23
Rockville, Maryland 20857

99 AUG 16 P2:25 0110

Your Re: Laxative Drug Products for Over-the-Counter Human Use
Proposed Amendment to the Tentative Final Monograph
Re: Use of Senekot for Bowel Management With
Imperforate Anus

Dear Sir or Madam:

I am the mother of Zachary, a 7½ years old who was born on January 24, 1992, with imperforate anus. Zack had surgery to create a temporary colostomy on his second day of life, since his congenital defect resulted in the absence of an anal opening, amongst other aspects.

Zack, (just as other children with his defect and vaster related defects) required additional surgeries to correct his malformation. His second surgery was a posterior sagittal anorectaplasty, to create an anal opening and realign the muscles

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of the bowel tract, to make a connection of bowel tract and anus. His third surgery was required to form rectal muscle. The final surgery was performed to close the colostomy. The pediatric surgeon who performed all surgeries with the exception of the final was Dr. Alberto Pena, Chief of Surgery, at Schneider Children's Hospital, Long Island Jewish Medical Center in New Hyde Park, New York.

Notwithstanding the surgeries, Zachary carries with him with him for life three (3) aspects of the malformation which could not and can never be corrected. They are: 1) low mobility, 2) reduced muscle functioning; and 3) lack of exquisite sensation. All of these characteristics relate to my extreme concern about your Administration's proposed final monograph for over the counter laxative drugs, including senna amongst other products.

As a result of Zachary's low bowel mobility, he is unable to have a complete bowel movement naturally. His body, without the aid of laxatives, works so as to produce small bowel movements all day long, instead of one or two sizeable ones. Because of the reduced muscle functioning and lack of exquisite sensation, he does not feel

the small movements all day and is prone to accidents i.e. it makes him incontinent. Upon the advice of Dr Peña, we began working on Zachary's bowel management with diet. We were unable to achieve any regularity with diet alone, therefore we began using Colace. My son (age 4 at the time) found the taste of colace to be totally distasteful, particularly in the quantities that he needed to take to achieve any result. (I literally had to force it into him.) In light of these facts we discontinued use after a very short time.

After that effort we attempted to have Zach eat Metamucil wafers, again with no success. Finally we began giving Zach Senekot tablets. We increased the dosage gradually to a total of 4 tablets per day, which we need to crush and mix with chocolate ice cream. Most fortunately Zachary has experienced regular bowel movements since beginning this regime of daily Senekot use. He takes the dosage in the morning which enables him to have one or two large bowel movements later in the day.

After reviewing the Notice of Proposed Rules appearing in the Federal Register: June 19, 1998

(Volume 63 Number 178) I am very concerned about your Department's proposed action for Sorbitol, which seems to fall into the category of laxative drug product for over the counter use. Any restricted availability of Sorbitol for my son would have a devastating effect upon the quality of his daily life. From my reading of the above referenced data, it appears that your Department is ~~[illegible]~~ considering restricting availability without any clear evidence that Sorbitol is cancer causing. Even if the proposed restriction would allow distribution by prescription, such action may have the net effect of removing the product from the market if the manufacturer decides that it could not maintain sufficient sales, if only by prescription.

In the event that my son is not able to have access to Sorbitol, our next step is to progress to a regime of daily Enemas which would be maintained for life.

My question is whether persons in my son's category (anorectal malformations) were given any consideration whatsoever, when the rule referenced was proposed? I

seriously doubt it is the case that they were.

Dr. Pena has performed in excess of 700 surgeries on persons born with anorectal malformations. Many of them are in my son's same situation. I urge you to consider them with great seriousness before taking further action.

Also, there is a support group for persons with my son's defect and related anorectal defects, called the Pull-Thru-Network, which is a chapter of the United Ostomy Association. I urge you to contact them or Dr. Pena for more information.

In a world where tobacco has not yet been banned or restricted although proven to be cancer causing, I implore you to act with the highest of due diligence before restricting something that is critical to the daily functioning of so many persons who have been visited with serious medical limitations from the moment of their birth, which limitations will

follow them throughout their lives.

Thank you for your attention to this matter. I ask that you kindly respond to acknowledge receipt of this correspondence. Should you require anything further relating to the above, I will gladly furnish same as quickly as possible.

Very truly yours,

Marylou Paul Chase

cc. Dr. Alberto Pena
Scott Bramlaw, President Pull-Thru Network
4 Woody Lane Westport, Conn. 06880
Senator Frank Lautenberg
Senator Robert G. Torricelli
Congresswoman Marge Roukema
Congressman Steven Rothman

FDA on Senator

[Federal Register: June 19, 1998 (Volume 63, Number 118)]
[Proposed Rules]
[Page 33592-33595]
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Parts 310 and 334

[Docket No. 78N-036L]
RIN 0910-AA01

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Laxative Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is reopening the administrative record and proposing to amend the tentative final monograph (proposed rule) for over-the-counter (OTC) laxative drug products to reclassify the stimulant laxative ingredients aloe, bisacodyl, cascara sagrada, and senna (including sennosides A and B) from Category I (generally recognized as safe and effective and not misbranded) to Category III (further testing is required). FDA is issuing this proposed rulemaking after considering data and information on the safety of bisacodyl, senna, and two related stimulant laxative ingredients, danthron and phenolphthalein. This proposal is part of the ongoing review of OTC drug products conducted by FDA.
DATES: Submit written comments by September 17, 1998. Written comments on the agency's economic impact determination by September 17, 1998. New data by June 21, 1999. Comments on the new data by August 19, 1999.
ADDRESSES: Submit written comments and new data to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2307.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of March 21, 1975 (40 FR 12902), FDA published, under Sec. 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these classes. In the advance notice of proposed

rulemaking, the Panel recommended Category I status for the OTC stimulant laxative ingredients aloe, bisacodyl, cascara sagrada preparations, danthron, phenolphthalein, and senna preparations (40 FR 12902 at 12908 to 12910). The agency concurred with the Panel's Category I classification of these ingredients in the tentative final monograph published in the Federal Register of January 15, 1985 (50 FR 2124 at 2152 to 2156).

II. Danthron and Phenolphthalein

In the Federal Register of September 2, 1997 (62 FR 46223), the agency reopened the administrative record for this rulemaking, discussed the carcinogenic risk of danthron and phenolphthalein, and proposed to reclassify these two anthraquinone laxative ingredients from Category I to Category II (not generally recognized as safe and effective or misbranded). The agency is evaluating the data and comments submitted in response to that proposal and will discuss this subject further in a future issue of the Federal Register.

III. Bisacodyl

The FDA Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) has recommended that the anthraquinone laxatives (aloe, cascara sagrada, and senna) and bisacodyl be tested in the standard battery of genotoxicity tests and under the test conditions by which phenolphthalein was found to be positive (Ref. 1). Phenolphthalein and bisacodyl are diphenylmethane derivatives with a similar chemical structure and pharmacological characteristics. The CAC recommended the Syrian Hamster Embryo (SHE) cell transformation assay as an early screen for bisacodyl and, based on its results, either the p53 transgenic mouse assay or another in vivo alternative assay, as appropriate, follow. Two-year carcinogenicity studies would then be contingent upon the results of these assays.

The agency has informed industry that additional testing for bisacodyl will be necessary (Ref. 2). Subsequently, industry submitted data from two mutagenicity studies (Ames test and rat bone marrow micronucleus assay) and a chromosomal aberration study in Chinese hamster ovary cells. The agency has reviewed these studies and determined that the results of all of the tests were negative (Ref. 3). Phenolphthalein was tested in two of these tests and was found negative in one (Ames test). However, findings from further studies indicated that phenolphthalein presents a potential carcinogenic risk. Thus, because of the chemical similarity of bisacodyl to phenolphthalein and the lack of previous carcinogenicity testing of bisacodyl, the agency is requesting that bisacodyl undergo further testing to assess its carcinogenic potential. Industry has completed dose range finding studies intended to select bisacodyl doses for a 6-month oral gavage carcinogenicity study in the p53 transgenic mouse (Ref. 4).

IV. Senna

The agency has reviewed metabolic, genotoxicity, and carcinogenicity data on senna and its components (Ref. 5). Senna contains a number of components, including but not limited to: Sennosides A and B, sennosides C and D, rhein (including rhein anthrone-8-monoglucoside and rhein-8-monoglucoside), chrysophanol, emodin, and aloe-emodin. The metabolic studies show that varying amounts of senna and its metabolites are absorbed into the

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systemic circulation. The data do not present conclusive absorption

information, nor indicate whether any of the metabolites present a safety hazard, if absorbed.

The agency believes that there are sufficient mutagenicity (Ames test) data in the literature on the senna extracts sennosides A and B, aloe-emodin, chrysophanol, and emodin. The data indicate that sennosides A and B are negative, while the senna extracts aloe-emodin, emodin, and chrysophanol are positively genotoxic (Ref. 5). Thus, senna preparations containing any of these components (or kaempferol or quercetin) may have mutagenic properties. These potentially mutagenic anthrones are found in the dried leaves and pods of senna. Therefore, until manufacturers can show that commercially available senna preparations do not contain mutagenic/genotoxic components, the agency is unable to state that sennosides A and B do not pose a relative risk to humans.

The agency also reviewed a 2-year carcinogenicity study with sennosides in the rat (Ref. 6). However, the agency found this study deficient because of the limited and incomplete histopathologic examination of tissues (Ref. 5). The agency concludes that further testing is necessary to assess the carcinogenic potential of senna products. In these studies, specific analysis of the test substance should be done to enable quantitative estimation of each component of the preparation. The senna dose selection should be based on a 1-month dose ranging study for an alternative assay or a 3-month dose ranging study for a 2-year carcinogenicity study in the rodent species and strains selected for the carcinogenicity studies. Histopathologic examination of all tissues from all groups of animals should be conducted (Ref. 5).

V. Aloe and Cascara Sagrada Preparations

Aloe and cascara sagrada are other anthraquinone ingredients. Cascara sagrada ingredients included in the tentative final monograph are casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract (50 FR 2124 at 2152). The agency has not received any mutagenicity, genotoxicity, or carcinogenicity data for these ingredients. The agency concludes that these ingredients need to have these types and other toxicity data using tests similar to those used and found positive for phenolphthalein.

VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. MM13, Docket No. 78N-036L, Dockets Management Branch.

2. Letter from D. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association (NDMA), coded LET111, Docket No. 78N-036L, Dockets Management Branch.

3. Letter from D. Bowen, FDA, to L. Totman, NDMA, coded LET175, Docket No. 78N-036L, Dockets Management Branch.

4. Comment No. C178, Docket No. 78N-036L, Dockets Management Branch.

5. Letter from D. Bowen, FDA, to J. Conover, The Purdue Frederick Co., coded LET173, Docket No. 78N-036L, Dockets Management Branch.

6. Comment No. LET113, Docket No. 78N-036L, Dockets Management Branch.

VII. Summary of the Agency's Changes to the Proposed Rule

The agency is proposing to reclassify the stimulant laxative

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